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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,803	07/22/2002	Gilles Caut	017753-160	2729

21839 7590 07/01/2004

BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER

RAMIREZ, DELIA M

ART UNIT PAPER NUMBER

1652

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary**Application No.**

10/089,803

Applicant(s)

CAUET ET AL.

Examiner

Delia M. Ramirez

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 April 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17,20 and 24-36 is/are pending in the application.
- 4a) Of the above claim(s) 31,33 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 17,20,24-30,32,34-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>4/26/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Application

Claims 17, 20, 24-36 are pending.

Applicant's amendment of claims 17, 20, 24-32, cancellation of claims 18-19, 21-23, and addition of claims 34-36, in a communication filed on 4/26/2004 are acknowledged.

As indicated in a previous Office Action mailed on 1/30/2004, claims 31 and 33 were withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to an invention non-elected with traverse in a communication filed on 11/12/2003. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 4/26/2004 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Objections

2. Claim 17 is objected to due to the recitation of "DHEA". Abbreviations unless otherwise obvious and/or commonly used in the art, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. It is suggested that the term "dehydroepiandrosterone" be used at least once followed by its abbreviation in parentheses. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 26 is indefinite in the recitation of “wherein said dehydrogenase activity is 17 β -hydroxysteroid...which catalyzes the production of a steroid precursor at position 17” for the following reasons. The term “position 17” refers to a specific location within the structure of a chemical compound. Therefore, it is unclear how an enzyme can catalyze the production of a compound at a position within the structure of a chemical compound. For examination purposes, it will be assumed that the term reads “wherein said dehydrogenase activity is 17 β -hydroxysteroid dehydrogenase activity which catalyzes the production of a steroid precursor hydroxylated at position 17”. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 17, 20, 24-30, 32 remain rejected and newly added claims 34-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in a previous Office Action and is applied to the claims above for the reasons of record and those set forth below.

8. Applicants argue that the claims as amended are adequately described. In particular, Applicants refer to Example 8 which discloses the claimed method practiced with *S. cerevisiae* cells and submit that *Saccharomyces* strains deficient in APAT activity can be readily generated since a number of routine techniques are available for inactivating expression. Furthermore, Applicants submit that the specification teaches how to generate APAT deficient yeast strains.

9. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 17, 20, 24-30, 32 or avoid the rejection of newly added claims 34-36. While it is agreed that (1) the claims are now limited to *Saccharomyces* cells and rat *cyp7b* genes, (2) the specification discloses practicing the claim method with *S. cerevisiae* cell, and (3) discloses references which show how to produce APAT-deficient *S. cerevisiae* cells by inactivation of the *S. cerevisiae atf2* gene, the Examiner disagrees with Applicant's contention that the instant claims are adequately described. It is noted that no structural limitations have been recited in regard to the rat *cyp7b* gene, *atf2* gene or the *yil124w* gene. Therefore, claims 17, 20, 25-30, 32, 34-36 require a genus of rat *cyp7b* genes, a genus of *Saccharomyces atf2* genes, and encompass any number of modification such that APAT activity is eliminated. Claim 24 requires a genus of rat *cyp7b* genes and a genus of *Saccharomyces atf2* genes. Claims 28, 34-35 also require a genus of *Saccharomyces yil124w* genes and encompass any number of modifications such that 17 β -hydroxysteroid dehydrogenase activity is eliminated. While the specification teaches the claimed method using *S. cerevisiae* transformed cells using the rat *cyp7b* gene having the structure disclosed in Stapleton et al., and further modified such that the *S. cerevisiae atf2* gene and the *S. cerevisiae yil124* gene are inactivated by an insertion or a deletion, the specification fails to disclose the structures or the structural elements which are common to (1) any rat *cyp7b* gene, (2) any *Saccharomyces atf2* gene, or (3) any *Saccharomyces yil124w* gene. Furthermore, the specification provides no teaching as to other methods to eliminate APAT or 17 β -hydroxysteroid dehydrogenase activity in addition to inactivation of the corresponding genes, such as structural modification in the gene structure to encode

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APAT or 17 β -hydroxysteroid dehydrogenase polypeptides with little or no activity, structural modifications in the transcriptional regulatory elements of the corresponding genes, or the addition of inhibitors of APAT or 17 β -hydroxysteroid dehydrogenase activity. As indicated previously, a sufficient written description of a genus of polynucleotides may be achieved by a recitation of a representative number of polynucleotides defined by their nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, there is no structural feature recited in the claims which is representative of all members of the genus of polynucleotides required to practice the claimed method and modify the claimed cells. The genus of polynucleotides required to practice the claimed invention is potentially a large and structurally variable genus. The specification only discloses one rat cyp7b gene, one *S. cerevisiae* atf2 gene, one *S. cerevisiae* yil124w gene, and one method to eliminate enzymatic activity, i.e. inactivation of the corresponding gene by an insertion or a deletion, which is insufficient for one of skill in the art to conclude that the claimed invention is adequately described.

10. It appears that the sequence listing does not disclose the structures of the rat cyp7b gene, the *S. cerevisiae* atf2 or the yil124w genes. It is noted that if the claims are further amended to recite the structures of the rat cyp7b gene and the *S. cerevisiae* atf2 gene, support for an amended sequence listing introducing the structures of the rat cyp7b gene and the *S. cerevisiae* atf2 gene appears to be present in page 4, lines 27-35 (Stapleton et al.; incorporated by reference) and page 7, lines 12-21 (Cauet et al., Eur. J. Biochem 261:317-324, 1999; incorporated by reference).

11. Claims 17, 20, 24-30, 32 remain rejected and newly added claims 34-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a *S. cerevisiae* yeast cell transformed with the rat cyp7b gene having the structure disclosed in GenBank's accession number U36992 (Stapleton et al.), and further modified such that the *S. cerevisiae* atf2 gene is inactivated by a

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deletion, and (2) a method for producing hydroxylated and/or acetylated steroids from DHEA or pregnenolone using *S. cerevisiae* cells, wherein said cells (a) have been transformed with the rat *cyp7b* gene having the structure disclosed in GenBank's accession number U36992, (b) have the *S. cerevisiae* *atf2* gene inactivated by a deletion, and (c) have the *S. cerevisiae* *yii124w* gene inactivated by an insertional mutation, does not reasonably provide enablement for (1) a method for producing hydroxylated and/or acetylated steroids from DHEA or pregnenolone with a *Saccharomyces* cell wherein said cell is (a) transformed with any rat *cyp7b* gene, (b) modified in any way to lack APAT activity, and (c) modified in any way to lack 17 β -hydroxysteroid dehydrogenase activity, or (2) a *Saccharomyces* cell modified in any way to lack APAT activity and further transformed with any rat *cyp7b* gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection has been discussed at length in a previous Office Action and is applied to the claims above for the reasons of record and those set forth below.

12. Applicants argue that the claims as amended are enabled. In particular, Applicants refer to Example 8 which discloses the claimed method practiced with *S. cerevisiae* cells and submit that *Saccharomyces* strains deficient in APAT activity can be readily generated since a number of routine techniques are available for inactivating expression. Furthermore, Applicants submit that the specification teaches how to generate APAT deficient yeast strains.

13. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 17, 20, 24-30, 32 or to avoid the rejection of newly added claims 34-36. As indicated above, the instant claims require a genus of polynucleotides and modifications not disclosed by the specification. While it is agreed that the art teaches some techniques for inactivating expression of a given gene, it is noted that these techniques require knowing something about the structure of the gene to be inactivated. As discussed previously, the specification does not provide the structures of all the

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Saccharomyces genes required such that inactivation by insertions or deletions can occur. Furthermore, as indicated above, the claims not only encompass elimination of activity by insertions/deletions in the target gene (i.e. inactivation) but they also encompass other modifications not described in the specification, such as specific structural changes in the gene of interest such that the protein encoded by such gene no longer has activity, structural changes in the promoter region such that transcription of the target gene is eliminated, or the use of inhibitors of the target activity. In addition, while the claimed invention requires a rat cyp7b gene, the specification does not disclose the structural elements which are associated with any rat cyp7b, such that one of skill in the art can determine whether a rat gene is a cyp7b gene. It is reiterated herein that while one could argue that the structures required to practice the claimed invention can be isolated by structural homology, the art clearly teaches many examples which demonstrate the unpredictability of assigning function based solely on structural homology. See particularly the teachings of Witkowski et al., Seffernick et al. and Broun et al. already discussed. Some teaching or suggestion as to how structure correlates with function is required. Therefore, in view of the information provided by the specification, and the unpredictability of the art regarding the isolation of the required polynucleotides based solely on structural homology, one cannot reasonably conclude that the claimed invention is enabled for the full scope of the claims.

Allowable Subject Matter

14. Claims 17 and 32 would be allowable if the claims are amended to (1) incorporate the structure of the rat cyp7b gene using a sequence identifier, (2) clearly state that the modification resulting in lack of APAT activity is due to the disruption (i.e. inactivation) of the *S. cerevisiae* atf2 gene, and (3) limit the cells to *Saccharomyces cerevisiae*. Claim 28 would be allowable if the claim contains all the limitations of claim 17 as indicated above and is further amended to clearly state that the modification resulting in lack of 17 β -hydroxysteroid dehydrogenase activity is due to the disruption of the *S. cerevisiae* yil124w

gene. Claims 17, 32 and 28 may be allowable with a broader scope in regard to the cells used, i.e. *Saccharomyces*, if the claims are amended as indicated above except for (3), and structural limitations are recited in regard to the *atf2* and *yil124w* genes, such that only those *Saccharomyces* cells which have *atf2* and *yil124w* genes with the structural limitation recited are encompassed by the claims. The structural limitations recited must be representative of all the members of the genus of polynucleotides required to practice the invention. If the claims are amended to recite structural limitations, care should be taken such that the amendments are supported by the specification and no new matter is introduced.

Conclusion

15. No claim is in condition for allowance.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

17. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be

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retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.


18. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
June 21, 2004


HELECA E. PRIDDY
PRIMARY EXAMINER
GROUP 1600
16-00